REMARKS

Claims 1-6, 8, 15-17, 87-88 and 90-92 are pending.

The claims are not amended.

The Applicants respectfully request reconsideration of this application.

Interview Summary

Examiner Horlick is thanked for the in-person interview with Applicant's representative James S. Keddie on April 7, 2008.

Possible unexpected results were discussed.

Although no agreement was reached, the Examiner indicated that he may withdraw the rejection if the Applicants make a showing of unexpected results.

The references discussed in this response will be filed in an Information Disclosure Statement.

Rejection of claims under 35 U.S.C. § 103 – Strutt in view of Schena

Claims 1-6, 8, 15-17, 87, 88 and 90-92 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Strutt (EMBO J. 1997 16: 3621-3631) in view of Page (US 5,871,920) or Guilfoyle (US 5,376,549) and Schena (Tibtech (1998) 16:301-306). The Applicants respectfully traverse this rejection.

It is well established that a *prima facie* case of obviousness can be successfully rebutted by evidence of unexpected results. See, e.g., Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007 / Notices at 57529, citing *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1395 (US 2007) and MPEP § 2141.V, also citing *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1395 (US 2007). See also MPEP § 716.02, et seq.

The Applicants submit that the labeling method recited in the rejected claims provides unexpectedly uniform labeling of genomic DNA. For this reason, it is believed that this rejection may be withdrawn.

This labeling method recited in the claims, which is referred to as the "LM-PCR" method in the specification, is shown below:

> i. blunting said DNA fragment to produce blunt ends;
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> ii. ligating adaptors to said blunt ends;
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> iii. amplifying said DNA fragment using a primer that binds to said adaptors; and
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> iv. labeling said DNA fragment either during or after said amplifying to produce a labeled DNA fragment;

The Applicants believe that this method unexpectedly provides uniform labeling of the entire genome and, as such, the claimed method works better than would be expected. This unexpected result of the LM-PCR labeling method is explicitly acknowledged on page 18, lines 7-10 of the specification:

> Four features of the global location profiling method were found to be critical for consistent, high-quality results. First, DNA microarrays with consistent spot quality and even signal background play an obvious role. An example of an image generated by the technique described herein is shown in figure 5A. Second, the LM-PCR method described herein was developed to permit reproducible amplification of very small amounts of DNA; signals for greater than 99.9% of genes were essentially identical within the error range when independent samples of 1 ng of genomic DNA were amplified with the LM-PCR method (Figure 5B). Third, each experiment was carried out in triplicate, allowing an assessment of the reproducibility of the binding data. And fourth, a single-array error model described by Hughs et al. (2000) was adopted to handle noise associated with low intensity spots and to average repeated experiments with appropriate weights

Emphasis added by Applicants.

Paraphrasing the above, the specification states that when a sonicated genome is labeled by the LM-PCR method and hybridized to an array, the signals from 99.9% of the features on the array were essentially identical. The Applicants believe that such a high level of uniformity would be unexpected.

The Applicants submit that the LM-PCR labeling method provided unexpectedly uniform labeling because the art at the time of filing is replete with

articles stating that PCR does not amplify uniformly. This phenomenon is commonly referred to "amplification bias".

A review of the literature at and prior to the time of filing of the instant application indicates that amplification bias was a well known phenomenon. For example, Warnecke (Warnecke et al, Nuc. Acids Res. 1997 25: 4422-4426) states that "PCR bias is sequence dependent and often strand specific" in the abstract and "it is possible that one population of sequence may amplify preferentially, leading to a PCR and an inaccurate estimate" in the first paragraph of the introduction. Likewise the Barnard's entire article (Barnard et al, Biotechniques 1998 25: 684-691) discusses the problems that PCR bias causes in cancer diagnostics. Likewise, Liu (Liu et al, Biotechniques 1997 22: 292-294) investigates how a single point mutation in the middle of a gene can cause a "dramatic inhibition" of PCR of that gene. Polz (Polz et al, Appl. and Env. Microbiol. 1998 64:3724-3730) discusses problems with amplifying rDNA from a mixed sample. "PCR selection" and "PCR drift" are seen as the main culprits. Finally, Suzuki (Suzuki Appl. and Env. Microbiol. 1998 64: 4522-4529), with reference to rDNA states "PCR dramatically biased the frequency distribution among gene homologs relative the original mixture". Many other references report the same phenomenon.

Given that many of the early studies were on a "gene-by-gene" bases, it is difficult to predict the exact percentage of sequences that would be affected by amplification bias on a genomic scale, and how affected they would be. Nevertheless, at the time of filing several researchers in the gene expression array field had noted that PCR bias was widespread in terms of the overall number of sequence it effects, and significant in that it significantly skews results. For example, with reference to gene expression studies Ji (Ji et al, J. Struct. Funct. Genomics 2000 1:1-7) states that PCR bias is unpredictable and a concern for gene expression studies.

See Ji's abstract:

mRNA. Collective PCR amplification of minute quantities of mRNA has great potential for overcoming these limitations. However, there remains significant concern about the effects of amplification on the absolute and relative abundance of individual mRNAs that could complicate subsequent gene expression studies. To address this problem, we systematically compared the relative abundance of many specific mRNAs from complex cDNA preparations (from tissue and cultured cells) both before and after amplification by PCR. Our results demonstrated that, as expected, the absolute abundance of different mRNAs in a cDNA library is altered in an unpredictable manner by PCR amplification.

underlining added.

Likewise, Lockhart in a seminal publication on array technology (Lockhart Nature 2000 405: 827-836) stated PCR is non-uniform in the sense that "the relative abundance of the cDNA products is *not* well correlated with the original mRNA levels" (emphasis added). See Lockhart page 833, middle of left hand column:

are two primary approaches that show significant promise. The first is a PCR-based approach that has been used to make single-cell cDNA libraries[76–78]. We have found that the amplification is efficient and reproducible, but that the relative abundance of the cDNA products is not well correlated with the original mRNA levels (D. Giang and D. J. Lockhart, unpublished results), although normalization and referencing strategies can be used (D. de Graaf and E. Lander, personal communication).

underlining added

Because PCR appears to be biased, PCR appears to have been abandoned for many gene expression studies in favor of linear amplification methods, e.g, those that that use T7 RNA polymerase or another polymerase.

Moreover, one of skill in the art would have no expectation that the LM-PCR methods of Page or Guilfoyle, cited in this rejection to provide that method, would result in uniform amplification. While the "blunting" step performed by Page and Guilfoyle may indeed increase the efficiency of ligation of sonicated fragments to a blunt end, there would be no reason to think that the blunting step would result in uniform amplification. In other words, incorporation of Page or Guilfoyle's method into that of Strutt might be expected to increase ligation efficiency and therefore

produce more starting product. However, it does not necessarily follow that the method would reduce amplification bias. More ligation does not necessarily mean uniform amplification.

At this point, the Examiner may be question as to how the recited labeling method results in uniform amplification. It is the Applicant's understanding that the reason why the method works is not known. In this regard, the Examiner is reminded that it is well established that an understanding of the scientific theory or principle underlying an invention is not a requirement for patentability.[1] Thus, while the exact molecular mechanism that provides uniform amplification may be an interesting topic for discussion, any assertions regarding the molecular mechanism of why the method works have no bearing on the patentability of the rejected claims.

Given the above, one of skill in the art would expect the labeling method recited in the rejected claims – which relies on PCR – to amplify non-uniformly. Thus, it was quite unexpected that claim recited labeling method resulted in highly uniform labeling.

Finally, while the Applicants believe that a declaration should be unnecessary given the above, the Applicants submit a Declaration under 37 C.F.R. § 1.132 by Dr. John Wyrick (the "Wyrick Declaration II"), the first named inventor in this application. In his declaration, Dr. Wyrick confirms that success of the claim-recited amplification method was quite unexpected, and states his reasons why.

Finally, as the Examiner no doubt knows, under the case law and its own rules of practice, the Office is required to consider the factual evidence in the record, including the Wyrick Declaration II and its factual underpinnings, and either accept them as true or rebut them with a factual showing of its own. *In re Alton*, 76 F.3d 1168, 1175, 37 U.S.P.Q.2d (BNA) 1578, 1583 (Fed. Cir. 1996). In this case, the Examiner may not be able to provide a rebuttal of either the findings or the conclusion presented by Dr. Wyrick in his declaration. If that is the case, Dr. Wyrick's declaration should carry full weight. Further, the Wyrick Declaration II cannot be dismissed merely because Dr. Wyrick is an inventor.

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[1] See, e.g., In re Gazave, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967); In re Chilowsky, 229 F.2d 457, 462, 108 USPQ 321, 325 (CCPA 1956) and Philip Morris, Inc. v. Brown & Williamson Tobacco Corp., 641 F. Supp. 1438, 1483 n.13, 231 USPQ 321, 355 n.13 (M.D. Ga. 1986).

The Applicants believe that an adequate showing of unexpected results is provided herein. A Notice of Allowance is respectfully requested.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone James Keddie at (650) 833 7723.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10050560-1.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: April 14, 2008

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